REMARKS

I. Status of the Application

This paper responds to a Non-Final Office Action, which was mailed on March 17, 2003. As originally filed, the Application included claims 1-7. In response to an Office Action mailed April 17, 2000, which rejected all of the claims, Applicant amended claims 1 and 3 and added claims 8-20. A subsequent Final Office Action, which was mailed on February 9, 2001, maintained the rejection of claims 1-7, rejected newly added claims 8-10, and withdrew from consideration claims 11-20 as being drawn to a non-elected invention. Following the February 9, 2001 Final Office Action, Applicant filed an After Final Amendment, which was not entered. On May 7, 2001, Applicant filed a Continued Prosecution Application, together with a Preliminary Amendment that amended claim 1 and cancelled claims 8 and 9. An Office Action mailed on August 15, 2001, again rejected claims 1-7 and 10. Applicant filed a response on December 17, 2001, presenting arguments regarding patentability. A Final Office Action was mailed on April 16, 2002, which maintained the rejection of claims 1-7 and 10. In response, Applicant submitted an After Final Amendment on June 13, 2002, which was refused entry in a subsequent Advisory Action. Applicant filed a Request for Continued Examination (RCE) on July 16, 2002. As part of the RCE, Applicant submitted an After Final Amendment, which amended claim 1. On December 11, 2002, Applicant responded to a Species Election Requirement that was mailed on November 12, 2002.

The present paper amends claim 1 and adds no new claims. The current Non-Final Office Action withdrew claims 6 and 7 from consideration. Accordingly, claims 1-5 and 10 are under currently under consideration. Applicant respectfully requests reconsideration of the pending claims in view of the above amendment and the following remarks. By action taken here, Applicant in no way intends to surrender any range of equivalents beyond that needed to patentably distinguish the claimed invention as a whole over the prior art. Applicant expressly reserves all such equivalents that may fall in the

range between Applicant's literal claim recitations and combinations taught or suggested by the prior art.

II. Amendment of Claim 1

The amendment clarifies that the invention is a solid particulate dispersion, which comprises crystalline particles of a pharmaceutical agent that are dispersed in a matrix to enhance the dissolution rate of the pharmaceutical agent in water. The matrix directly contacts the pharmaceutical agent and consists of at least one water-soluble polymer. The amendment also recites that the solid dosage form is made by mixing the pharmaceutical agent and the polymer at a temperature sufficiently high to melt or soften the polymer, but insufficiently high to melt the pharmaceutical agent. This ensures that the pharmaceutical agent retains the form of crystalline particles after being dispersed in the polymer matrix. The specification, as filed, fully supports the changes to claim 1, and therefore the amendment introduces no new matter. See, for example, Application at page 1, line 26-page 2, line 11; page 6, lines 23-32; page 8, line 1-page 9, line 20; page 12, Table 1, and lines 19-22.

III. Rejection of Claims 1-5 and 10 Under 35 U.S.C. §§ 102, 103

The Non-Final Office Action rejected claims 1, 3, 5 and 10 under 35 U.S.C. § 102 as being anticipated by WO 96/25149, and rejected claims 1-5 and 10 under 35 U.S.C. § 103 as being unpatentable over WO 96/25149in view of U.S. Patent No. 5,478,852 to Olefsky. Applicant respectfully traverses the rejections.

Applicant submits that WO 96/25149 and Olefsky '852, either alone or in combination, do not teach or suggest every limitation of claim 1, and therefore the references neither anticipate nor render obvious the claimed invention. For example, neither reference discloses a "solid particulate dispersion" comprised of "crystalline particles" of a pharmaceutical agent, which are "dispersed" in a matrix consisting of at least one water-soluble polymer in order to enhance the dissolution rate of the pharmaceutical agent in water. Olefsky '852 provides no details on the nature of the solid form preparations, and at most, WO 96/25149 discloses what is described below as a

"solid dispersion" or "solid solution," which is different than the "solid particulate dispersion" recited in the claims of the present application. Although WO 96/25149 discloses melt extrusion, nothing in the reference indicates that the pharmaceutical agent does not melt during processing. Instead, WO 96/25149 discloses that it is "generally customary to melt a physical mixture of ancillary substances, active ingredients and polymers together." WO 96/25149 at page 6, lines 1-3.

Furthermore, a close examination of the other references cited in the present case illustrates similar differences between the references and the claimed invention. For instance, Example I of WO 93/11749 discloses an amorphous (non-crystalline) pharmaceutical agent (romglizone) that is dissolved in a matrix. According to WO 93/11749, a solid dispersion is a "pharmaceutical formulation which may be defined as 'a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting the two (fusion), dissolving them in a solvent, or a combination of approaches, i.e., a quasi melting-solvent method'." WO 93/11749 at page 1, lines 19-24. In other words, solid dispersions are solid solutions in which a pharmaceutical agent is dissolved in an inert carrier or matrix so that the pharmaceutical agent no longer exists as crystalline particulate. WO 93/11749 inventors were able to obtain a solid dispersion through the use of a "plasticizer/solubilizer," explaining that the "surprising and unexpected results of the present [WO 93/11749] invention is the creation of a solid pharmaceutical dispersion comprised of the aforementioned water insoluble drugs and carriers without the need for using organic solvents, fusion (heat) or both (solvent/heat) . . . Surprisingly, it was discovered that the addition of a plasticizer/solubilizer during the mixing of the two components results in a chemical environment that readily lends itself to dispersion formation." WO 93/11749 at page 6, line 32-page 7, line 6. Thus, whereas WO 93/11749 discloses an amorphous pharmaceutical agent dissolved in a matrix that includes a plasticizer/solubilizer, the claims of the present application recite a solid particulate dispersion comprised of crystalline particles dispersed in a matrix consisting of one or more water-soluble polymers.

Reference JP 5-4919 (Chemical Abstracts No. 240956) and reference WO 95/32713 (Chemical Abstracts No. 156003) disclose "solid dispersions" or "solid solutions," which are not the same as the "particulate dispersion" recited in claim 1 of the present application. For example, JP 5-4919 discloses "solid dispersions contain[ing] thiazolidines . . . dispersed in water-sol. polymers" that were obtained by "dissolv[ing the thiazolidines and polymers] in a mixt. of 100 g acetone and 100 g EtOH." JP 5-4919 Abstract. Similarly, WO 95/32713 discloses a "solid dispersion . . . [of] a thiazolidine deriv." that was obtained by admixing "hydroxypropylmethyl cellulose 0.02, dichloromethane 20, and ethanol 20 g . . . to dissolve [the thiazolidine derivative and hydroxypropylmethyl cellulose]." WO 95/32713 Abstract. Although the JP 5-4919 and WO 95/32713 references describe dosage forms comprised of particles, neither document discloses particles of a crystalline pharmaceutical agent dispersed in a matrix as required by claim 1 of the present application. Instead, JP 5-4919 describes spraying the thiazolidine/polymer/acetone/EtOH solution on croscarmellose Na to make granules, and WO 95/32713 describes evaporating dichloromethane and ethanol to yield solids "which are pulverized to give fine particles." JP 5-4919 Abstract and WO 95/32713 Abstract. However, in JP 5-4919 and WO 95/32713 the pharmaceutical agent (thiazolidine derivative) remains dissolved in the polymer.

U.S. Patent No. 5, 641,516 to Grabowski et al. also discloses "solid dispersions" or "solid solutions." According to Grabowski '516, the "particular active substance can be present in the compositions according to the invention in amorphous form, virtually homogeneously dispersed in the melt, which is advantageous for evenly delayed release and good absorption. The substances which are present as a molecular dispersion in a polymer melt are normally also called 'solid solutions'." Grabowski '516 at col. 3, lines 3-8 (emphasis added). The pharmaceutical agent of Grabowski '516 is not dispersed as discrete crystalline particles in a matrix as required by the claims of the present application, but instead, the pharmaceutical agent exists as a "molecular dispersion in a polymer melt." Although Grabowski '516 arguably discloses the use of water-soluble polymers, an express objective of the compositions disclosed in Grabowski '516 is to

delay the release of active substance, not enhance to enhance the dissolution rate of the pharmaceutical agent. Therefore, not only does Grabowski '516 fail to disclose crystalline particles dispersed in a matrix, it teaches away from the present invention.

EP 0137198 fails to disclose a "solid particulate dispersion" of a crystalline pharmaceutical agent, but instead discloses "solid dispersions" or "solid solutions" similar to the references described above. For example, EP 0137198 discloses a "solid dispersion composition," which can be prepared by "dissolving dihydropyridine A compound in suitable organic solvent, adding a water-soluble polymer, hydroxypropylmethyl cellulose, to the resultant solution to prepare homogeneous suspension, and then evaporating the organic solvent according to the conventional manner." EP 0137198 at page 2, lines 17-23. Like JP 5-4919 and WO 95/32713, the solid dispersion disclosed in EP 0137198 can be "converted to various dosage forms such as powders, fine granules, granules," but such particles do not comprise a substantially crystalline pharmaceutical agent coated by a matrix as required by claim 1 of the present application. Instead, the pharmaceutical agent (dihydropyridine A) remains dissolved in hydroxypropylmethyl cellulose.

EP 0552708 also fails to disclose a "solid particulate dispersion" of a crystalline pharmaceutical agent, but instead concerns "solid dispersions" of an amorphous active ingredient. Indeed, EP 0552708 deals with "solid dispersions," which are "defined as a technology for dispersing a drug monomolecularly in a solid state into an inert carrier . . . [using] a solvent process, a fusion process, . . . [or] a mixed-grinding process (mechanochemical process)." EP 0552708 at page 2, lines 9-13 (emphasis added). Moreover, EP 0552708 describes a process for converting a "sparingly water-soluble drug to an amorphous state and the dispersion of the drug in this amorphous state into the carrier . . . ." EP 0552708 at page 2, lines 43-48. Indeed, as noted in EP 0552708, thermal "analysis of the solid dispersions obtained by the method of the invention in [EP 0552708] . . . using differential scanning calorimetry revealed disappearance of the endothermic peak of the sparingly water-soluble drug, indicating that the sparingly water-soluble drug was made amorphous to give a solid dispersion." EP 0552708 at page 3,

lines 27-30 (emphasis added). In EP 0552708, the pharmaceutical agent is not dispersed as discrete crystalline particles in a matrix as required by the claims of the present application, but is an "amorphous" material dispersed "monomolecularly in a solid state into an inert carrier."

EP 0580860 also fails to disclose a "solid particulate dispersion" of a crystalline pharmaceutical agent, but instead relates to a "process for producing a solid dispersion," which is a "drug-containing pharmaceutical bulk substance comprising the drug dissolved or dispersed in a polymer." EP 0580860 at page 2, lines 3-7 (emphasis added). The disclosed process results in solid dispersions having x-ray diffraction (XRD) patterns similar, if not identical, to solid dispersions made using a conventional solvent technique. See, for example, Figs. 2, 4, 7, 9, and 11 of EP 0580860, including the brief description of the drawings at page 13, line 29-page 14, line 49. Significantly, the XRD patterns in each of the figures indicate that in all cases, the disclosed process has converted the pharmaceutical agent (compound A, indomethacin, nifedipine, oxybutynin HCl, or diclofenac sodium) from crystalline form (lowest pattern in each figure) to an amorphous form (top two patterns of each figure).

Thus, in contrast to the solid dispersions (solutions) disclosed in the references, the present application discloses and claims a solid particulate dispersion in which crystalline particles of the pharmaceutical agent are dispersed in a matrix. None of the examples in the present application include a plasticizer/solubilizer so that throughout processing the pharmaceutical agent remains in the form of crystalline particulate. Indeed, the sharp peaks of the XRD patterns shown in FIG. 1-FIG. 7 of the present application indicate that the bulk of the pharmaceutical agent remains crystalline following manufacture of the solid particulate dispersion.

IV. Conclusion

In view of the foregoing, Applicant respectfully submits that all pending claims are patentable over the prior art of record. If the Examiner has any questions, Applicant requests that the Examiner telephone the undersigned.

Applicant believes that any fees required to file the present amendment have been identified in a transmittal that accompanies this paper. However, if any fees are required in connection with the filing of this paper have not been identified in the accompanying transmittal, please charge deposit account number 23-0455.

Respectfully submitted,

Date: July 16, 2003

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